DETAILED ACTION

Application Status

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/04/2009 has been entered.

Applicants' amendment canceling Claims1-94; amending Claims 100-104, 106-107, 110-114, 120-124, 126 and 130-135; and added Claims 136-138 in the paper of 06/04/2009 is acknowledged. Claims 95-138 are pending in the instant office action and will be examined herein.

Withdrawn-Claim Objections

2. The previous objection of Claims 96, 106 and 126 for reciting "wherein the pH is 8.6" or "wherein the pH is 8.5" is withdrawn by virtue of applicants' amendment.

Withdrawn-Claim Rejections - 35 USC § 112 – 1st paragraph

3. The previous rejection of Claims 100-104, 110-114, 120-124 and 130-135 under 35 U.S.C. 112, first paragraph, **new matter**, as failing to comply with the written description requirement, is withdrawn by virtue of applicants' amendment.

4. The previous rejection of Claims 95-135 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by reconsideration of the Examiner.

5. The previous rejection of Claims 95-135 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn by reconsideration of the Examiner.

Claim Rejections - 35 USC § 112 – 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 136-138 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argument relevant to the instant rejection has been considered from the Remarks filed on 6/4/2009. Applicants argue, in view of four species disclosed in the specification, the "application contemplates multiple and more generic infliximab crystals and methods of preparing infliximab crystals; thus one skilled in the art would understand the Applicants are in possession of the invention as broadly claimed (see

bottom of page 14 to top of page 15, Remarks filed on 6/4/2009). The examiner acknowledge the argument above if the species disclosed in the specification are representative species of claimed genus or the said four species provide the correlation between the structure and function of claimed genus. However, because the four species disclosed in the specification are not representative species of claimed genus as noted below; and do not teach the structure of infliximab crystal and/or the function of forming said crystal; thus can not provide the correlation between the structure and function of claimed genus for the reasons stated below in more details.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The recited term "infliximab" has been interpreted according to the specification's disclosure at p. 98, paragraph [0272], which states, "Infliximab is a chimeric murine/human monoclonal antibody commercially available as Remicade™. (Centocor, Leiden, the Netherlands). This monoclonal antibody has been widely used to treat rheumatoid arthritis and Crohn's disease. Infliximab is a chimeric IgG1 kappa immunoglobulin that binds to the TNF-A antigen. It is composed of murine light- and heavy-chain variable region sequences and a human constant region sequence. The Infliximab antibody has an approximate molecular weight (MW) of 149 kD". The instant specification teaches four infliximab compositions as described in Examples of 34-37.

However, the breadth of claims includes genus of any possible form of infliximab crystals or any infliximab comprising any constituent(s); and methods of making said any possible form of infliximab crystal (i.e., Remicade™) or methods of crystallizing any possible infliximab comprising any constituent(s) including, but not limited to, any buffer and/or any crystallizing solution. The instant specification discloses four specific infliximab crystal having certain constituents composition [i.e., (1) ethoxyethanol, lithium sulfate and Tris buffer; (2) PEG-400, lithium sulfate and Tris buffer; (3) PEG MME 550, Calcium chloride and Tris HCl; (4) PEG 300, Tris buffer, PEG 8000 and glycerol]. The prior art does not teach any representative species of infliximab crystals (or a method of forming said crystal thereof) encompassed by the genus of the claims. Thus, the instant specification alone or in combination with the prior art does not describe sufficient species for the claimed genus for one skilled in the art to possess the claimed inventions; and does not describe the correlation between the structure of constituents

(e.g., chemical structure) in claimed infliximab crystals (or a method of forming said crystal thereof) with the "function" of crystallization of said infliximab to form said any infliximab in crystalline form. In order for a broad generic claim to satisfy the written description requirement, the specification must provide adequate description in the specification to reflect the variation in the genus by describing a sufficient number of representative species. In Regents of the University of California v. Eli Lilly & Co. the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d 1601; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Thus, the species which are described in the specification are not deemed to be representative of claimed genus of infliximab antibody crystals and methods for which the claims are drawn to because these representative species fail to reflect the wide variation among the members of the genus. Because the Claims have very wide structural limitation (having unlimited infliximab crystal structure or having unlimited added constituent(s), for example) with no functional correlation (i.e., being able to form a crystal) in the claimed genus, the one skilled in the art would not be in possession of full scope of the claimed genus of the instant specification.

7. Claims 136-138 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for four specific infliximab crystal having certain constituents composition [i.e., (1) ethoxyethanol, lithium sulfate and Tris buffer; (2) PEG-400, lithium sulfate and Tris buffer; (3) PEG MME 550, Calcium chloride and Tris HCl; or (4) PEG 300, Tris buffer, PEG 8000 and glycerol]; **does not** reasonably provide enablement for any possible form of infliximab crystals, any infliximab crystals having any buffer or any crystallizing solution, or method of forming said crystals thereof.

Applicants argument relevant to the instant rejection has been considered from the Remarks filed on 6/4/2009. Applicants argue, in regard to the breadth of the claims, the specification at pages 98-99 provides examples that teach methods of infliximab crystallization (see page 10, lines 15-16, Remarks filed on 6/4/2009). However, as noted below, the Examiner acknowledges the species disclosed by the instant specification but they are not representative of claimed genus and does not teach direction and guidance. Applicants argue, in regard to the nature of the invention, the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art (see page 11 of Remarks filed on 6/4/2009), that it appears the Office's position stems from concerns that can arise in preparing single large crystal for X-ray crystallographic studies. However, the Examiner is aware of the situation that instant crystal is not drawn to the crystal for the X-ray crystallography; and instant rejection is directed to a crystal and a method of forming the crystal thereof which is not used in X-

ray crystallography because the consideration of crystal claims and method thereof in terms of preparing crystal for X-ray crystallographic studies would be different from the instant rejection and would need different requirement to overcome the instant rejection. Applicants argue, in regard to the amount of direction provided by the inventor, the existence of working examples, that applicants provided actual working examples and the specification also provide guidance as to how to crystallize infliximab as shown on page 67, lines 23 to page 75, line 5; wherein the actual reduction to practice is not required prior to filing. Applicants further argue, in regard to the quantity of experimentation needed to make or use the invention based on the content of the disclosure, that office must consider all the evidence related to each of these factors and any conclusion of non enablement must be based on the evidence as a whole; and argue that the application was sufficient to teach one of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation (see page 13 of Remarks filed on 6/4/2009). The Examiner acknowledges that actual reduction to practice of claimed invention is not required if sufficient direction and guidance has been provided for one skilled in the art to make and use the claimed invention without undue experimentation (emphasis added); which is not the case in the instant application for the reasons below. The Examiner acknowledges that instant application teach four species among the claimed genus and enables one skilled in the art to make and use said four species among the claimed genus. However, as noted below, and as acknowledged by applicants, the key word is "undue". As noted below, one skilled in the art would require undue experimentation because the crystallization of

any infliximab antibody crystal is highly unpredictable and difficult; and one skilled in the art would require undue experimentation to make and use the claimed genus other than said four species disclosed in the application by the instant specification.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The breadth of the claims: Claims 136-138 are drawn to the breadth of claims includes genus of any possible form of infliximab crystals and methods of making said any possible form of infliximab crystal (i.e., Remicade™) or methods of crystallizing any

possible infliximab comprising any constituent(s) including, but not limited to, any buffer and/or any crystallizing solution.

The nature of the invention: The invention is related to antibody crystals of infliximab, also known commercially as Remicade™ (assuming the brand name antibodies has not been modified over time) and a method of forming said crystals thereof as shown in the Examples 34-37 on pages 98-99; wherein the infliximab is dissolved in a solution containing 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate and 6.1 mg dibasic sodium phosphate prior to setting up crystallization. Three infliximab crystals have used tumbling of crystallization solution to make infliximab crystal. However, the ability to crystallize a given antibody (which is an example of protein or polypeptide comprising amino acid) was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in failure to form a crystal of infliximab as described below.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: In the instant case, the quantity of experimentation would be overly large because the smallest change in ***any*** parameter in crystallizing a protein/antibody can have enormous consequences. Thus, one crystallization condition known to work does not enables the crystallization of a related/similar protein/antibody or 'native' protein/antibody. Rather, what would be required is precise instruction about how to make the each and every protein/antibody crystal (each and every one); thus, can not avoid undue experimentation for any form of infliximab crystal other than the condition that is known to work. The instant specification and prior art also provide no

direction or guidance on how a skilled artisan might achieve crystal growth of Infliximab in any conditions (having any other molecule(s) and/or any other buffer(s), for example). The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein/antibody does not necessarily works for another, and what works for one native protein or antibody does not necessarily work for a mutant or fragment even though they essentially contain the same protein/antibody that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein and/or antibody (see Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22, as cited previously).

At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a fortuitous role in obtaining successful crystallization conditions despite the extremely high skill level of those in the art. For example, Drenth describes a case where it seemed impossible to successfully crystallize a particular protein they were working on until the air conditioner in the laboratory broke down over night thereby increasing the temperature in the lab to the "correct temperature" which was needed to induce successful crystal growth (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2, as cited previously). This is

just one example out of the many countless tales of the unpredictability of the art. As cited previously on pages , Klyushnichenko (Curr. Op. Drug Discovery, 2003, 6(6):848-54) teaches (p. 849, 1st column, 2nd paragraph, as cited previously):

> The objectives of a bulk protein crystallized process are to rapidly purify and concentrate the produce with high yield and without loss in potency. However, crystallization has not been used widely in the purification or formulation of biological compounds. *This is due to the difficulties in developing crystallization conditions that are reproducible and scalable at clinical- and commercial-scale*."
>
> As discussed above, there are several examples of large-scale protein crystallization; however, researchers frequently report that no clear understanding of the protein crystallization mechanism has yet emerged. Typically several hundred experiments must be performed to determine crystallization conditions, such as pH, buffer type, precipitant type and protein concentration. To control costs and improve efficiency, it is important to minimize the number of experiments, especially if the final or intermediate conditions are to be scaled-up.

Furthermore, more specifically in term of antibody crystal and a method of forming the crystal thereof, Yang et al. (who is one of instant inventor, PNAS June 10, 2003, Vol. 100, pages 6934-6939) disclose the unpredictability and difficulty in making antibody in crystalline form (see bottom of left column to top of right column, on page 6934). Thus, the crystallization of protein (including antibody) is difficult and unpredictable and the number of experimentation required to make and use the claimed invention is high.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only four working example of the claimed crystal of infliximab and the method of crystallization thereof. See specification pages 98-99.

Prior art does not teach the crystallization of infliximab having composition recited in claims. Other than these four working examples, the specification and prior art fail to provide guidance for altering the crystallization conditions for crystallizing any form of infliximab crystal or any infliximab crystal comprising any constituent(s) other than (1) ethoxyethanol, lithium sulfate and Tris buffer; (2) PEG-400, lithium sulfate, and Tris Buffer; (3) PEG MME 550, calcium chloride and Tris HCl buffer; or (4) PEG 300, Tris buffer, PEG 8000, and glycerol.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these crystallization conditions are specific to a particular protein or antibody. Thus, a skilled artisan is left to experiment by a trial and error process to determine other conditions (i.e., other than the four specific condition noted above) for crystallization; thus, no sufficient direction and guidance can be provided for crystallizing any form of infliximab crystal or any infliximab crystal with any other constituents.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make any possible form of infliximab crystal or any infliximab crystal with any constituents (and methods of forming said crystals thereof which is very broad infliximab crystal encompassed by the instant claims 136-138), undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 136 and 138 are rejected on the ground of nonstatutory double patenting over claims 35 of U. S. Patent Application No. 10/741,861 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the US patent application and the application are claiming common subject matter, as follows: Instant claims 136 and 138 encompasses any form of infliximab antibody crystal or any infliximab antibody having any constituents (buffer and salt, for example) which are anticipated by the crystalline spherical Infliximab in Claim 35 of U. S. Patent Application No. 10/741,861 (see the most recently filed Claims on 6/27/2008).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656